Drinking Water Source and Chlorination Byproducts I. Risk of Bladder Cancer

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We conducted a population-based case-control study of bladder cancer in Iowa in 1986–1989 to evaluate the risk posed by tapwater containing chlorination byproducts. We combined information about residential history, drinking water source, beverage intake, and other factors with historical data from water utilities and measured contaminant levels to create indices of past exposure to chlorination byproducts. The study comprised 1,123 cases and 1,983 controls who had data relating to at least 70% of their lifetime drinking water source. After we adjusted for potential confounders, we calculated odds ratios for duration of chlorinated surface water of 1.0 (referent), 1.0, 1.1, 1.2, and 1.5 for 0, 1–19, 20–39, 40–59, and ≥60 years of use. We also found associations with total and average lifetime byproduct intake, as represented by trihalomethane estimates. Positive findings were restricted to men and to ever-smokers. Among men, odds ratios were 1.0 (referent), 1.1, 1.3, 1.5, and 1.9, and among ever-smokers, 1.0, 1.1, 1.3, 1.8, and 2.2, after adjustment for intensity and timing of smoking. Among nonsmoking men and women, regardless of smoking habit, there was no association. Among men, smoking and exposure to chlorinated surface water mutually enhanced the risk of bladder cancer. The overall association of bladder cancer risk with duration of chlorinated surface water use that we found is consistent with the findings of other investigations, but the differences in risk between men and women, and between smokers and nonsmokers, have not been widely observed. (Epidemiology 1998;9:21–28)

Keywords: bladder neoplasms, water, chlorination, case-control study, gender, trihalomethane, smoking, drinking water source.

Chlorination byproducts are found in drinking water disinfected with chlorine. Byproduct levels in treated surface waters are much higher than in groundwater supplies, owing to higher concentrations of organic precursors.[1,2] Ecologic studies[3–7] have indicated a link between chlorination byproducts and elevated bladder cancer risk, as have case-control studies based on death certificate records.[8–10] Additionally, four case-control studies of incident bladder cancer and a longitudinal investigation gathered individual data on exposure and disease status, permitting adjustment for risk factors such as smoking and occupation.[11–15] These studies found relative risks in the range of 1.5- to 2-fold among those with long-term use of chlorinated surface water sources, compared with no exposure to chlorinated surface water. Nevertheless, the modest elevations in risk, various methodologic limitations, and differences in populations and water source quality among these studies left several issues unresolved.[16] Moreover, there is a need to replicate these findings in other settings. We therefore conducted a population-based case-control study of incident cancer in the state of Iowa. Bladder cancer, the subject of this report, was one of six cancer sites investigated. Colon and rectal cancers are the subject of a companion report.[17]

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Methods

Study Population

Eligible cases were residents of Iowa, ages 40–85 years, newly diagnosed with histologically confirmed bladder cancer in the years 1986–1989, and without previous diagnosis of a malignant neoplasm. We identified cases through the State Health Registry of Iowa, the statewide tumor registry, supplemented by a rapid reporting system during 1987 and 1989. We selected controls under 65 years of age from computerized state driver's license records and controls 65 years old and older from U.S. Health Care Financing Administration listings. We excluded as controls persons with a previous cancer diagnosis. The study was conducted in two phases. In the first phase (1986–1987), bladder cancer was one of six

cancer sites, and we frequency-matched controls, by sex and 5-year age group, to all cases, resulting in a case: control matching ratio for the bladder cancer case series of approximately 2.3:1. In the second phase (1988–1989), we restricted the study to bladder cancer cases only and a control series, with frequency-matching of controls to cases at a ratio of 1:1. We included cases of both *in situ* and invasive bladder cancer (transitional cell carcinoma and papillary transitional cell carcinoma) because they appear to share the same risk factors.[18,19] We included patients diagnosed in 1987 with *in situ* disease in the 1988–1989 study period, resulting in more cases in the second (N = 894) than the first phase (N = 558).

Data Collection and Study Subjects

After obtaining physician consent (for cases), we sent a letter to study subjects explaining the study and inviting participation. In a subsequent telephone call, we requested completion of a postal questionnaire. The questionnaire included demographic information, smoking history, occupational history, and other life-style and medical items. We also asked about adult fluid consumption frequency, inside and outside of the home, of beverages using tapwater (water *per se*, coffee, hot and iced tea, reconstituted fruit juices, fruit drinks from powdered mixes, and soups from concentrate or dry mix), and other beverages. We gathered a lifetime residential history, with water source at each place. Subjects provided the name of each city or town of residence for at least 1 year, the period of residence, and the primary source of drinking water as a private well, community supply, bottled, or other (specified). We also requested the geographic location and water source at all places of employment, for jobs held at least 5 years.

We offered hesitant subjects a 15-minute telephone interview, omitting the detailed occupational history and other items not central to the analysis of water quality. We screened returned questionnaires for complete responses to several key items, including residential/water supply history, cigarette smoking history, and fluid ingestion, and we retrieved missing information by telephone.

Response Rates

We identified 1,716 eligible bladder cancer cases, of whom 84.6% (1,452) participated by completing a mail questionnaire (N = 1,309), a full-length telephone interview (N = 87), or an abbreviated telephone interview (N = 56). Among cases, 156 respondents (10.7%) were proxies for subjects who had died or were not competent to participate. Among controls younger than age 65 years, we selected 999 eligible subjects from state driver's license listings, and 81.8% (817) participated. We selected 2,034 eligible controls age 65 years and older from Health Care Financing Administration listings, and 79.5% (1,617) participated. Of the 2,434 participating controls, 2,164 completed a mail questionnaire, 102 a telephone interview, and 168 an abbreviated telephone interview. All control questionnaires (with two exceptions) were completed directly by study subjects.

Survey of Water Purveyors

In the spring and summer of 1987, we conducted a survey of all Iowa water utilities that served at least 1,000 persons,[20] collecting historical information from 280 utilities serving 345 Iowa communities with a total 1980 population of 1.94 million (state population = 2.92 million). Most of the state population not served by these community supplies used private wells. Trained employees of the University of Iowa Hygienic Laboratory personally interviewed the water plant operator at each utility, using a structured questionnaire. The interviewers requested information on sources and treatments of drinking water used by the utility since its inception. Information was supplemented by data from the State Department of Health (Division of Public Health Engineering), the Iowa Department of Natural Resources (Geological Survey Bureau), and a 1979 historical survey of Iowa communities conducted as part of the National Bladder Cancer Study.[11,20]

Trihalomethane Measurements

At each water utility, the interviewer collected one or two samples from the clear well (where water enters the distribution system) or from nearby in the system. Samples were collected in duplicate 40-ml vials with Teflon lids; sodium thiosulfate was added to quench further byproduct formation, and the samples were analyzed at Iowa's University Hygienic Laboratory, using U.S. Environmental Protection Agency (EPA) method 524.2 (including all required quality control measures) for the presence and concentration of chloroform, bromodichloromethane, dibromochloromethane, and bromoform.[21] This method is a gas chromatography-mass spectrometric technique using purge and trap sample concentration and introduction, with a minimal detection limit of 1 μg per liter.

Exposure Indices

We combined information from the water utility survey, our trihalomethane (THM) measurements of water samples, and personal questionnaire data (residential history and tapwater consumption) to create indices of exposure for each study respondent. We developed two general classes of exposure index: The first comprised measures for duration of water use from (1) chlorinated surface sources, (2) chlorinated ground sources, and (3) any chlorinated water source; the second comprised estimates of lifetime (or shorter time period) intake of

TABLE 1. Geometric Mean Levels (μg/Liter) of Total Trihalomethanes in 222 Iowa Water Supplies, by Source of Water and Presence and Type of Chlorination Treatment, 1987*,†

Type of Water Source and Well Depth (ft)	Type of Treatment		
	No Chlorination	Prechlorination/Prefiltration Chlorination and Postchlorination	Postchlorination (Only)
Surface	NA‡	73.89 (20)	38.09 (10)
Ground			
<51	0.63 (3)	13.82 (6)	3.15 (16)
51–150	0.61 (7)	2.03 (13)	3.92 (30)
151–500	0.50 (9)	1.80 (17)	1.43 (32)
>500	0.50 (5)	0.65 (23)	0.91 (31)

* Number of water utilities used to calculate the average is in parentheses.
† When the level of measured trihalomethanes was below the analytical detection limit, we used a value of 0.5 μg per liter in the calculation of the geometric mean value.
‡ NA = not applicable.

trihalomethanes—both total integrated intake and time-weighted average concentration.

To develop estimates of THM exposure, we summed the concentrations (of chloroform, dibromochloromethane, bromodichloromethane, and bromoform) from the analyzed water samples from the 222 water utilities that had a single water source and one type of treatment. In multivariate models, we found that total THM in finished water was determined primarily by (1) water source (surface [river, stream, lake, reservoir] or ground); (2) if a ground source, the well depth; and (3) the location in the treatment process of chlorine addition. Table 1 shows geometric mean values of total THM from these 222 supplies by source type and treatment. In calculating geometric means, we used a value of 0.5 μg per liter for instances with THM concentrations below the 1.0 μg per liter detection limit. THM levels were generally higher in samples from surface than groundwater, higher in shallow than deep wells, and higher when chlorine was added at an early stage (prechlorination) than only at a late stage of water treatment (postchlorination). We estimated past levels of total THM in each Iowa water supply by applying the geometric mean levels from Table 1 to the respective type of water source(s) and treatment(s) used historically. If a water supply used more than one type of source or treatment in a given year, THM averages were weighted by the estimated amount of water contributed by each source. We merged these historical estimates with individual residential histories and combined them with information on tapwater consumption to develop indices of total lifetime THM ingestion (gm) and time-weighted average THM exposure (μg per liter). We ignored missing data in the calculation of the time-weighted averages.

Statistical Analysis

We used odds ratios (ORs) to estimate the association between various measures of exposure and bladder cancer risk.[22,23] We adjusted OR estimates for several known or suspected bladder cancer risk factors using unconditional logistic regression analysis with case-control status as the response variable. The ratio of controls to cases differed by study period, so we included an indicator variable for period in logistic regression models to adjust for this difference. Where appropriate, we adjusted for sex, age (four categories: 40–54, 55–64, 65–74, 75–85 years), cigarette smoking (never, two categories of ex-smokers, three categories of current smokers), years of education (five categories), and employment (ever) in an occupation associated with elevated bladder cancer risk (sex-specific) in the literature.[24] In evaluating trend, we entered the exposure measure as a continuous variable. We used additional measures of duration and intensity of cigarette smoking in specific analyses. Tests of linear trend and of homogeneity of trend were based on standard score statistics.[25]

We established a cutoff for inclusion in the analysis at 70% or more of lifetime years with available information on drinking water source. We selected the cutoff after balancing missing data against the number of subjects with useful information. We lacked information about type of water source during periods when (1) residential information was missing or type of water source was not reported; (2) the subject resided outside of Iowa and used a community water source; or (3) the subject used a community water source in Iowa located in a small town (population <1,000) not included in our water utility survey. The analysis database numbered 1,123 cases [77.3% of all study case respondents, 875 men (77.1%) and 248 women (78.2%)] and 1,983 controls [81.4% of all control respondents, 1,308 men (81.7%) and 675 women (81.0%)].

Results

Table 2 shows selected characteristics of subjects included in and excluded from the analysis. Subjects in the analysis group were slightly older and less well educated, and they had smoked somewhat less than excluded respondents. Relative risk estimates within the analysis and the excluded groups were similar for most risk factors (controlling for age, sex, and study period).

The median diagnosis age was 68 years (in the study population that excluded patients under 40 years of age). Overall, there were nearly four times as many male (N = 1,135) as female (N = 317) subjects. As reported elsewhere, cigarette smoking was associated with bladder cancer. Smokers were defined as "current" if actively smoking at diagnosis (cases) or interview (controls), or if they had stopped within the preceding 2 years. The odds ratio for ever holding a job generally associated with bladder cancer in other studies[24] was 1.3 in the analysis population and 1.7 in the excluded group. After adjustment for age, smoking, occupation, and other risk fac-

TABLE 2. Characteristics of Cases and Controls in the Study Population. Data Are Presented Separately for Respondents Included in the Analysis (Source of Drinking Water Was Ascertained for at Least 70% of Lifetime), or Not Included (All Others)*

	Percentage of Lifetime at a Known Water Source					
	≥70% (Included in Analysis)			<70% (Not Included in Analysis)		
Characteristic	Cases (%)	Controls (%)	OR (95% CI)	Cases (%)	Controls (%)	OR (95% CI)
Total	1,123	1,983		329	451	
Age (years)						
40–54	107 (9.5)	189 (9.5)		46 (14.0)	53 (11.8)	
55–64	249 (22.2)	441 (22.2)		67 (20.4)	107 (23.7)	
65–74	415 (37.0)	738 (37.2)		137 (41.6)	167 (37.0)	
75–85	352 (31.3)	615 (31.0)		79 (24.0)	124 (27.5)	
Sex						
Male	875 (77.9)	1308 (66.0)		260 (79.0)	293 (65.0)	
Female	248 (22.1)	675 (34.0)		69 (21.0)	158 (35.0)	
Study period						
1986–1987	446 (39.7)	1229 (62.0)		112 (34.0)	274 (60.8)	
1988–1989	677 (60.3)	754 (38.0)		217 (66.0)	177 (39.2)	
Cigarettes: timing, daily amount (packs)						
Never-smoker†	271 (24.3)	934 (47.2)	1.00	61 (18.8)	173 (38.4)	1.00
Former, <1	137 (12.3)	232 (11.7)	1.82 (1.4–2.4)	38 (11.7)	61 (13.5)	1.62 (1.0–2.8)
Former, ≥1	301 (27.0)	451 (22.8)	2.05 (1.7–2.6)	100 (30.8)	115 (25.5)	2.18 (1.4–3.4)
Current, <1	96 (8.6)	112 (5.6)	3.06 (2.2–4.2)	19 (5.8)	29 (6.4)	1.78 (0.9–3.5)
Current, 1–<2	222 (19.9)	190 (9.6)	4.14 (3.2–5.3)	73 (22.5)	61 (13.5)	3.49 (2.1–5.7)
Current ≥2	87 (7.8)	61 (3.1)	5.29 (3.6–7.7)	34 (10.5)	12 (2.7)	8.00 (3.7–17.4)
Missing	9	3		4	0	
High-risk (*a priori*) occupation						
Never†	819 (72.9)	1560 (78.7)	1.00	223 (67.8)	354 (78.5)	1.00
Ever	304 (27.1)	423 (21.3)	1.26 (1.1–1.5)	106 (32.2)	97 (21.5)	1.72 (1.2–2.4)
Education (years)						
<9†	285 (25.7)	437 (22.2)	1.00	69 (21.3)	70 (15.7)	1.00
9–11	190 (17.1)	276 (14.0)	1.11 (0.9–1.4)	46 (14.2)	46 (10.3)	1.00 (0.6–1.8)
12 (high school)	400 (36.0)	776 (39.4)	0.81 (0.7–1.0)	118 (36.4)	146 (32.7)	0.74 (0.5–1.2)
13–15	149 (13.4)	297 (15.1)	0.85 (0.7–1.1)	43 (13.3)	88 (19.7)	0.45 (0.3–0.8)
≥ College	86 (7.7)	186 (9.4)	0.69 (0.5–0.9)	48 (14.8)	97 (21.7)	0.41 (0.2–0.7)
Missing	13	11		5	4	

* Odds ratios were calculated using logistic regression, with adjustment for age (four groups), sex, and study period (1986–1987 or 1988–1989).
† Referent category.

tors, no association with bladder cancer risk was found for average lifetime population size of the city or town of residence (data not shown). Data in subsequent tables are restricted to subjects in the analysis dataset.

We calculated the number of person-years of exposure experience for residences served by various types of drinking water supplies. There were 78,006 person-years among cases and 136,448 person-years among controls included in the analysis. The proportion of person-years with missing information was similar among cases (6.3%) and controls (5.5%). A small portion of exposure experience (0.5% among cases, 0.4% among controls) was at nonchlorinated surface water supplies, used occasionally in the past. The percentage of total person-years at chlorinated sources of water (both surface and ground) was greater among cases (41.1%) than among control subjects (37.3%). Chlorinated surface water, with higher THM levels, accounted for 12.3% of case and 11.1% of control population person-years. Residence at places served by chlorinated ground sources, with relatively low exposure to THM, accounted for 28.8% of case person-years and 26.2% of control person-years. Among cases, 51.8% of person-years were spent at residences with nonchlorinated groundwater sources, either private (42.9%) or public (8.9%). The comparable figures for control subjects were 56.4% of person-years with nonchlorinated groundwater sources, 47.5% private and 8.9% public. We assumed minimal exposure to chlorination byproducts for these years (THM below detection limit).

Table 3 shows ORs for bladder cancer risk by intake level of all beverages and by total tapwater intake. Results are adjusted for smoking, high-risk occupation, education, age, study period, and sex (where applicable). We found little association of risk with either measure, in men or women. We calculated our measure of "all beverages" consumption by summing the contributions of many types of beverages. When information about one or more beverages was not available, we did not calculate the sum, resulting in a relatively large proportion of subjects with an unknown level (31% of cases, 29% of controls).

Table 4 shows ORs by increasing duration of exposure to chlorinated surface water, chlorinated groundwater,

TABLE 3. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Bladder Cancer by Fluid Ingestion from All Beverages and from Beverages Made with Tapwater for Men, Women, and Both Sexes

Level of Consumption (Liters/Day)	Men			Women			Both Sexes: OR* (95% CI)
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	
All beverages							
<2.08†	117	221	1.00	40	134	1.00	1.00
2.08–<2.72	162	223	1.43 (1.0–2.0)	53	125	1.61 (1.0–2.7)	1.49 (1.1–2.0)
2.72–<3.46	140	228	1.08 (0.8–1.5)	52	129	1.16 (0.7–1.9)	1.13 (0.9–1.5)
≥3.46	181	254	1.13 (0.8–1.5)	31	91	1.08 (0.6–1.9)	1.14 (0.9–1.4)
Unknown	275	382		72	196		
P (trend)			0.76			0.82	0.60
Beverages from tapwater							
<1.58†	173	303	1.00	45	139	1.00	1.00
1.58–<2.13	183	282	1.18 (0.9–1.6)	57	154	1.18 (0.7–1.9)	1.18 (0.9–1.5)
2.13–2.85	208	289	1.22 (0.9–1.6)	74	154	1.44 (0.9–2.3)	1.30 (1.00–1.6)
≥2.85	217	298	1.18 (0.9–1.6)	48	136	0.99 (0.6–1.7)	1.15 (0.9–1.5)
Unknown	94	136		24	92		
P (trend)			0.45			0.52	0.28

* Logistic regression models included variables for the exposure (liters per day of total beverage or total tapwater intake), (sex), age (4 strata), study period, education, high-risk occupation, and cigarette smoking habit (6 strata).
† Referent category.

and any chlorinated water. It also shows ORs by estimated total lifetime ingestion of THM and time-weighted lifetime average THM exposure. The "never-used" exposure category for chlorinated surface water included subjects exposed to chlorinated groundwater for 1 year or more, and the comparable chlorinated groundwater stratum included persons exposed to surface water. We therefore adjusted the ORs for duration of chlorinated surface water by duration of chlorinated groundwater, and *vice versa*. Risk increased among men, but not women, with duration of chlorinated surface water, duration of chlorinated groundwater, and duration of any chlorinated water source. We found opposite trends in risk for men and women (*P* for trend 0.009 for men and 0.18 for women for exposure to chlorinated surface water). Overall, ORs increased with each of the measures of exposure duration to chlorinated water sources.

The results for total lifetime THM ingestion (gm) and time-weighted average lifetime THM level (μg per liter) paralleled the findings for chlorinated surface water duration, consistent with the strong correlation between the THM exposure estimates and duration measures of exposure. In addition to the THM-related exposures shown in Table 4, we evaluated risk associated with estimated THM intake or THM concentration within various time windows (5–19 years before diagnosis (or interview for controls), 20–39 years before, etc), or levels estimated for particular years (for example, 1950, 1960, 1970). Results were generally consistent with those shown.

In further analyses, we found that an association of bladder cancer risk with duration of chlorinated surface water use was present only among ever-smokers. There was no evidence of elevated risk among never-smokers. Restricting the analysis to ever-smokers, we computed ORs for chlorinated surface water using several logistic regression models that included different smoking measures. Changing the model by substituting various measures of duration and intensity of smoking had little impact on the OR point estimates or trends among ever-smokers. With no control for smoking intensity, for example, the ORs among smokers were 1.0, 1.1, 1.3, 1.7, and 2.1 for chlorinated surface water durations of 0, 1–19, 20–39, 40–59, and ≥60 years. Controlling for five levels of smoking [three levels current (<1 pack, 1-<2 packs, ≥2 packs) and two levels past (<1 pack, ≥1 pack], we found that ORs for duration of chlorinated surface water among smokers were 1.0, 1.1, 1.3, 1.6, and 2.2. In another model, we controlled for five levels of smoking duration and found ORs of 1.0, 1.1, 1.3, 1.5, and 2.2. Other levels of control yielded a similar result. All smoking-related measures that we used showed dose- or duration-related associations with bladder cancer (see, for example, Table 2). Trends in ORs with duration of chlorinated surface water were different between ever- and never-smokers [*P* (interaction) < 0.001]. Although data were limited, our analyses suggested that the increasing ORs for duration of surface chlorination source occurred primarily among male smokers (OR = 1.0, 1.1, 1.3, 1.8, 2.3), with little evidence of increased risk among men who had never smoked (1.0, 1.0, 0.7, 0.4, 1.2) or women, regardless of smoking status (smokers: 1.0, 1.2, 1.1, 0.8, 1.2; never-smokers: 1.0, 0.7, 0.4, 0.6, 0.5). Male smokers represented 65% of all cases. Among male cases, 84% had ever smoked, and among female cases, 53%.

In Table 5, we show the risk of bladder cancer in men by joint exposure to cigarettes and to years of chlorinated surface water. As noted above, we found no association among never-smoking men. ORs increased both with smoking level and among the ever-smokers, with duration of chlorinated surface water use. When we used other measures of cigarette smoking (such as duration or number of packs per day) in combination with the chlorinated surface water duration measure, we found similar results.

TABLE 4. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Bladder Cancer by Gender and Duration of Residences Served by Chlorinated Surface Water, Chlorinated Groundwater, or All Chlorinated Water Sources; and by Estimates of Total Lifetime Trihalomethane Intake from Water and Lifetime Average Total Trihalomethane Level*

Exposure Measure	Men			Women			Total: OR (95% CI)
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	
Chlorinated surface water (years)							
Never used†,‡	537	875	1.0	152	400	1.0	1.0
0–19	192	268	1.1 (0.8–1.3)	65	160	0.9 (0.6–1.4)	1.0 (0.8–1.2)
20–39	73	84	1.3 (0.9–1.8)	14	55	0.7 (0.3–1.3)	1.1 (0.8–1.4)
40–59	48	57	1.5 (0.95–2.3)	13	44	0.7 (0.3–1.4)	1.2 (0.8–1.7)
≥60	25	24	1.9 (1.1–3.6)	4	16	0.7 (0.2–2.4)	1.5 (0.9–2.6)
P (trend)			0.009			0.18	0.13
Chlorinated groundwater (years)							
Never used†,‡	251	443	1.0	61	181	1.0	1.0
0–19	216	328	1.1 (0.9–1.4)	52	172	0.8 (0.5–1.3)	1.0 (0.8–1.3)
20–39	261	330	1.4 (1.1–1.8)	71	200	0.9 (0.6–1.4)	1.3 (1.0–1.6)
40–59	132	188	1.3 (0.96–1.7)	58	112	1.1 (0.7–1.8)	1.3 (1.0–1.7)
≥60	15	19	1.4 (0.7–3.0)	6	10	1.6 (0.5–5.2)	1.5 (0.8–2.8)
P (trend)			0.04			0.10	0.008
All chlorinated water sources (years)							
Never used†	174	337	1.0	43	112	1.0	1.0
0–19	168	282	1.0 (0.8–1.4)	47	149	0.7 (0.4–1.1)	1.0 (0.8–1.2)
20–39	237	319	1.2 (0.9–1.6)	56	180	0.7 (0.4–1.1)	1.1 (0.9–1.4)
40–59	222	297	1.3 (1.0–1.7)	78	181	0.8 (0.5–1.3)	1.2 (0.9–1.5)
≥60	74	73	1.9 (1.3–2.8)	24	53	1.0 (0.5–2.0)	1.6 (1.2–2.3)
P (trend)			0.002			0.88	0.006
Total lifetime THM (gm)							
≤0.04†	257	478	1.0	67	203	1.0	1.0
0.05–0.12	234	323	1.3 (1.0–1.7)	66	162	1.2 (0.8–1.8)	1.3 (1.0–1.6)
0.13–0.34	115	181	1.1 (0.8–1.5)	44	111	0.9 (0.6–1.6)	1.1 (0.9–1.4)
0.35–1.48	133	187	1.2 (0.9–1.6)	41	104	1.0 (0.6–1.7)	1.1 (0.9–1.4)
1.49–2.41	43	62	1.3 (0.8–2.0)	12	35	0.9 (0.9–2.0)	1.2 (0.8–1.7)
≥2.42	60	56	1.8 (1.2–2.7)	10	41	0.6 (0.3–1.4)	1.3 (0.9–2.0)
Unknown	33	21		8	19		
P (trend)			0.05			0.54	0.08
Lifetime avg THM level (μg/liter)							
≤0.7†	269	501	1.0	71	194	1.0	1.0
0.8–2.2	244	314	1.3 (1.0–1.6)	68	181	0.9 (0.6–1.3)	1.2 (1.0–1.5)
2.3–8.0	123	188	1.1 (0.9–1.5)	42	110	0.8 (0.5–1.3)	1.1 (0.8–1.4)
8.1–32.5	133	194	1.1 (0.8–1.5)	44	103	0.9 (0.6–1.5)	1.1 (0.8–1.4)
32.6–46.3	53	54	1.7 (1.1–2.6)	11	45	0.6 (0.3–1.3)	1.3 (0.9–1.8)
≥46.4	53	57	1.5 (1.0–2.4)	12	42	0.6 (0.3–1.3)	1.2 (0.8–1.8)
P (trend)			0.02			0.33	0.04

* From a logistic regression model that included (sex), age, study period, education, high-risk occupation, and cigarettes (6 strata). The model for chlorinated surface water included a variable for duration of chlorinated groundwater (5 strata), and *vice versa*.
† Referent category.
‡ The referent exposure level for chlorinated surface water use (nonusers) included users of chlorinated groundwater, and *vice versa*.

The pattern of findings shown in Tables 4 and 5 was unchanged when we restricted the analyses to the 1,006 cases (of 1,123) and 1,983 controls (of 1,984) who were direct, rather than proxy, respondents.

Discussion

We designed this study to evaluate the association of bladder cancer risk and exposure to chlorination byproducts in chlorine-disinfected drinking water. Our overall findings support the hypothesis of an association, but aspects of our results caution against a simple interpretation and raise additional questions about the nature of the link.

Chlorination byproducts were discovered in drinking water in 1974,[1,2] and numerous evaluations since have identified much higher levels in chlorinated surface water than in chlorinated groundwater, owing to higher levels of precursor organic chemicals in the former. A large body of evidence from laboratory studies shows that the byproduct mixture, and many component chemicals identified to date, are mutagenic and/or carcinogenic.[26–30] Thus, it is reasonable that many epidemiologic studies, this one included, employed "duration of chlorinated surface water use" as a surrogate of exposure. The setting of this study, Iowa, afforded the opportunity to also evaluate duration of chlorinated groundwater use. We detected an increase in bladder cancer risk with duration of chlorinated groundwater use, as well as with total duration of chlorinated drinking water (surface plus ground), with ORs similar to those observed with chlorinated surface water. This finding was unexpected because the levels of byproducts from most chlorinated groundwaters are much lower than levels in treated surface water. These findings may indicate that

TABLE 5. Odds Ratios (OR) and 95% Confidence Intervals among Men for Bladder Cancer by Cigarette Smoking (Never, Past, Current) and Duration of Residences Served by Chlorinated Surface Water Sources. The Numbers of Cases and Controls Are Shown in Brackets*

Years of Exposure to Chlorinated Surface Water	Smoking Status		
	Never-Smoker	Past Smoker	Current Smoker
None†	1.0‡ [112, 332]	1.7 (1.3–2.3) [236, 387]	3.5 (2.5–4.7) [188, 156]
1–19	1.0 (0.6–1.6) [27, 75]	1.9 (1.4–2.8) [92, 131]	3.5 (2.3–5.3) [73, 62]
20–39	0.8 (0.3–2.0) [6, 22]	2.0 (1.2–3.5) [30, 42]	5.7 (3.1–10.4) [37, 20]
≥40	0.7 (0.3–1.9) [5, 26]	3.5 (2.1–5.8) [39, 39]	5.8 (3.0–11.3) [29, 16]

* From a logistic regression model that included age, study period, education, high-risk occupation, and years of chlorinated groundwater use.
† The lowest exposure level for years of exposure to chlorinated surface water (none) included users of chlorinated groundwater.
‡ Referent category.

duration of exposure to byproducts is more important than byproduct level. In addition to chance, alternative explanations are (1) that THMs, the most readily measured of the chemicals comprising the mixture, are poor surrogates for one or more carcinogenic factor(s) in the chlorination byproduct mixture, or (2) that bladder cancer risk is related to levels of free chlorine, usually present at similar levels in disinfected waters from both surface and ground sources. When we used various estimates of lifetime THM exposure (whether total integrated dose or time-weighted average), associations with bladder cancer risk were weaker than when duration measures were used. This result was possibly due to misclassification of these exposures, or again, it may have occurred because exposure duration is more important as a predictor of risk. We were not able to estimate past mutagenicity of drinking water.[31] The historical water quality measures necessary to make such estimates were not available from most water utilities.

Our observation that risk increased with duration of chlorinated surface water among ever-smokers, but not never-smokers, and among men, but not women, raises questions of internal consistency, as well as consistency with other findings. In contrast to the current investigation, the National Bladder Cancer Study[11] found associations for both sexes, primarily among never-smokers. In Ontario, King and Marrett[13] noted somewhat higher risk estimates for never-smokers associated with duration of chlorinated surface water. In Colorado, McGeehin *et al*[12] reported similar patterns of risk among smokers and never-smokers, and among men and women. Finally, in a case-control study from Washington County, MD, Freedman *et al*[14] reported results that parallel the current findings, namely that the risk associated with chlorinated surface water was primarily observed among men and among smokers. Reasons for differences among these observations and differences with results from our study are unclear. A possible explanation for the apparent discrepancies in findings for smokers and never-smokers among studies may reside in water quality and water treatment differences in the respective study areas, with resulting variations in the chemical composition of byproduct mixtures.[32,33] Nevertheless, results should not differ by sex.

We found no link between tapwater intake and bladder cancer risk. Results from other investigations are equivocal. Several have found positive associations with intake of tapwater or total fluid,[11,12,34–36] and others found no link.[37–39] Our estimates of tapwater consumption level (median = 2.1 liters, with 1.7 liters consumed at home), were higher than those from the National Bladder Cancer Study[11] (median = 1.2 liters) and from a U.S. Department of Agriculture[40] random stratified survey of the U.S. population (median = 1.4 liters for adults ≥65 years old). The collection methods of these two surveys may have provided more accurate estimates of intake than did our postal questionnaire.

In addition to effects of tapwater *per se*, two case-control studies found that elevated risk with long-term exposure to water with elevated byproduct levels was enhanced among high-level tapwater consumers.[11,13] We did not find this pattern in Iowa. A positive association with tapwater consumption in Colorado was not modified by duration of chlorinated water exposure.[12]

Ours was a relatively large population-based case-control study with a response rate of over 80%. Controls under 65 years of age were selected from driver's license rosters, which in Iowa afford excellent coverage of the state population, with little or no urban/rural bias.[41] Health Care Financing Administration rosters, estimated in the past to cover 98% of the ≥65 population, were used to select controls over 65 years of age.[42] We were able to characterize water source for most of the lifetime of more than 80% of our subjects, and we demonstrated that the pattern of risk factors among subjects excluded from the analysis was consistent among cases and controls, and that the exclusions did not introduce bias.

Because many people are unaware of the source of their community drinking water, and most are unaware of the hypothesis of a link between water source and cancer risk, it is unlikely that cases and controls reported differently about their residential histories. It is unlikely that our findings among smokers were due to uncontrolled (residual) confounding by smoking-related exposures. Among smokers, control for duration, intensity, and currency of smoking (all of which showed dose-related associations with bladder cancer in our data) had little effect on the pattern of risk associated with chlorinated surface water duration. We were not able to distinguish clearly between the interactive effects of gender and smoking. Almost two-thirds of all cases were men who had smoked.

Our ability to adjust for job-related risk factors, beyond controlling for having ever been employed in a high-risk occupation, was limited. However, occupational exposures would have to be tightly linked with exposure duration to chlorinated surface water to contribute substantially to the monotonic increase of risk

that we found, an unlikely scenario. Eleven per cent of cases were represented by next-of-kin or other proxies, which might have introduced bias (essentially all controls were direct respondents). Results were similar, however, when proxy respondents were excluded.

Several areas of inquiry were not included in this study. One is the influence on bladder cancer risk of urinary stasis in relation to total fluid and tapwater consumption. Genetic differences in bladder cancer susceptibility are receiving increasing attention.[24] To the extent that interindividual variation exists in enzymes that activate or detoxify chlorination byproducts, an understanding of such differences could help identify populations at risk and broaden our knowledge of biological mechanisms. Further elucidation of this and other interactions is warranted.

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